**Alpha-defensin in synovial fluid as a new biomarker for the diagnosis of periprosthetic joint infection**

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**Objective:** Prosthetic joint infection (PJI) occurs after primary joint replacements at a rate of 1.0-2.5% and increases to 2.0-5.8% in revision surgeries. When treating a painful joint replacement, the ability to distinguish between septic and aseptic failure of the prosthesis is critical, as the treatment for PJI necessitates unique surgical strategies that aim to eradicate the organism. Currently, surgeons utilize a wide spectrum of tests in the attempt to diagnose PJI, including local measures of synovial inflammation (synovial fluid white blood cell count and differential, synovial tissue white blood cell count), systemic measures of inflammation (serum C-reactive protein level, erythrocyte sedimentation rate), radiologic tests (radiographs, bone scan), and bacterial isolation techniques (Gram stain, culture). Each of these methods individually has limitations for either sensitivity or specificity. It has been reported that 10-20% of all confirmed infections cannot be confirmed via culture methods. The failure of these tools to reliably diagnose infection, and the resulting clinician disparity in practice, recently led the Musculoskeletal Infection Society (MSIS) to publish a consensus definition of PJI, utilizing a combination of clinical data and six of the above tests.

**Methods:** We assessed the ability of alpha-defensin to distinguish prosthetic joint infection from aseptic inflammation utilizing a series of well-characterized samples that were clearly defined by the MSIS criteria utilizing an alpha-defensin ELISA (Hycult) modified for use with synovial fluid. The study included 23 aseptic samples and 22 septic samples that were provided by the Rothman Institute. Receiver Operating Characteristic (ROC) analysis was conducted to select the optimal cutoff for the assay and its performance was established verses the MSIS criteria. Additionally, the performance of each of the individual methods utilized in the MSIS criteria was evaluated utilizing the recommended criteria.

**Results:** A total of 45 well-defined samples were used to establish the optimal cutoff (7.7µg/mL) for the alpha-defensins using a ROC analysis that yielded an area under the curve (AUC) of 1.0. The sensitivity (and 95% confidence interval) for alpha-defensin, ESR, CRP, WBC count, PMN% and culture were 100% (84.6-100%), 95.5% (77.2-99.9%), 95.5% (77.2-99.9%), 95.5% (77.2-99.9%), 95.5% (77.2-99.9%) and 90.9% (70.8-98.9%) respectively. The specificity performances were 100% (85.2-100.0), 78.3% (56.3-92.5%), 87.0% (66.4-97.2%), 95.7% (78.1-99.9%), 95.7% (78.1-99.9%) and 95.7% (78.1-99.9%) respectively. There was significant separation between the positive and negative populations for alpha defensin where the concentration of the lowest positive sample was 2.44 fold higher than the highest negative sample.

**Conclusion:** The measurement of alpha-defensin levels provides a highly sensitive and specific method to aid the diagnosis of PJI with improved performance compared to the traditional methods utilized for the analysis of synovial fluid.